

The specification supports the amendments to claim 72 as shown by the following claim amendment chart:

<u>Claim Amendments</u>	<u>Applicant's Disclosure</u>
<p>72. . . .</p> <p>(a) transfecting somatic cells <i>in vitro</i> with a DNA sequence <u>by chemical or physical techniques</u></p> <p>. . . to introduce the DNA <u>sequence</u> into the cells . . .</p>	<p>An alternative approach for gene therapy involves introducing DNA into a cell by chemical, as opposed to viral, techniques. (Page 5, lines 8-10.)</p> <p>A third major current approach to gene therapy involves the use of physical techniques (Page 6, lines 5-6.)</p> <p>Physical techniques, though highly efficient, are at present incapable of application to the large numbers of cells which would need to be transfected in order to provide a reasonable therapy. (Page 6, line 31, through page 7, line 2.)</p> <p>Chemical procedures involve the introduction of DNA into a cell which had previously been extracted from a subject individual. (Page 7, lines 2-7.)</p> <p>In detail, the invention provides a method of altering the concentration of a desired gene product in a recipient subject which comprises providing to the recipient subject a transfected cell preparation, the preparation containing at least one transfected cell which contains a desired gene sequence, wherein the cell, when provided to the subject, will direct the expression of the desired gene sequence, thereby causing the production of a desired gene product. (Page 10, lines 1-9.)</p> <p>In one embodiment of the present invention, the desired or effector DNA sequences are introduced into the</p>

(b) screening the resulting transfected somatic cells *in vitro* to select a cell, wherein the selected cell is stably transfected with the DNA sequence by integration of the DNA sequence into the chromosome of the selected cell or in a replication competent plasmid to impart to the selected cell the permanent capacity to direct expression of the DNA sequence . . .

(d) [administering] injecting the resulting cloned and expanded cells [to] into the recipient subject;

wherein the DNA sequence comprises the gene and a promoter.

transfected cell (Page 19, lines 4-7.)

If such sequences integrate into the chromosome of the transfected cell or are able to replicate as extrachromosomal plasmids, then the cell may acquire the permanent capacity to direct the expression of the introduced, genetic sequence. Such a cell is said to be "stably transfected." (Page 33, lines 13-18.)

Since such cells acquire the permanent capacity to express the introduced genetic sequence, it would be preferable to employ stably transfected cells in situations in which one desired to provide the recipient subject with a prolonged capacity to produce the desired or effector gene product. (*Id.* at lines 18-24.)

Figure 2 shows the amount of human growth hormone detected in the bloodstream of mice which had received interperitoneal injections of either transiently transfected (dashed lines) or stably transfected (solid lines) cells. (Page 13, lines 7-11.)

Introduce Cells Into Desired Anatomical Location. (Fig. 1.)

In order to accomplish gene expression, it is necessary that the structural sequences of the desired of [sic, or] effector gene be operably linked to a promoter region. (Page 18, lines 28-31.)

Thus, any promoter capable of functioning in the transfected cell can be operably linked to the desired or effector gene sequence and used to express the

gene in the transkaryotic cell. (Page 19, lines 13-16.)

[Original claim] 3. The method of any one of claims 1-2 wherein said desired or effector gene sequence is operably linked to a constitutive promoter region. (Page 62, lines 20-22.)

[Original claim] 4. The method of any one of claims 1-2 wherein said desired or effector gene sequence is operably linked to a regulatable promoter region. (*Id.* at lines 23-25.)

wherein the promoter is not a retroviral promoter; and

In the past few years, it has become apparent that the implementation of retroviral based gene delivery systems will face major obstacles, primarily related to properties of retroviruses themselves (Robertson, M. Nature 320:213-214 (1986), Marx, J.L., Science 232:824-825 (1986)). First, it has not been generally possible to achieve expression of mammalian genes in the retroviral vectors used to infect human cells, and until this problem is solved, the issue of regulated gene expression cannot be addressed. (Page 4, lines 16-25.)

Among the preferred regulatable promoter regions which may be employed is the mouse metallothionein promoter region. (Page 19, lines 20-23.)

Alternatively, promoter regions which are regulatable by temperature (such as the *Drosophila* heat shock promoter), sugars (such as the yeast gal-4 promoter), double-stranded RNA, etc., may be employed. (*Id.* at lines 30-33.)

Plasmid pXGH5 contains the human growth hormone gene fused to the mouse metallothionein-I (mMT-I) promoter region. (page 40, lines 7-9.)

As described above, the plasmid pXGH5 contains the mouse metallothionein-I promoter. (page 44, lines 21-22.)

wherein, following injection into the recipient subject, the clonal cells are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences

In the past few years, it has become apparent that the implementation of retroviral based gene delivery systems in humans will face major obstacles, primarily related to properties of retroviruses themselves (Robertson, M., Nature 320:213-214 (1986), Marx, J.L., Science 232:824-825 (1986))

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Third, as recombination between the replication-deficient retroviruses utilized for the infection and the endogenous retroviruses present in mammalian genomes is known to occur (Hock, R.A. et al., Nature 320:275-277 (1986)), there is the potential of initiating a chronic retroviral infection in the host animal. (Page 4, line 16, through page 5, line 4.)

The use of viral vectors suffers from their potential for rearrangement of endogenous genes (Page 6, lines 27-31.)

and initiating chronic viral infection in the recipient subject.

Third, as recombination between the replication-deficient retroviruses utilized for the infection and the endogenous retroviruses present in mammalian genomes is known to occur (Hock, R.A. et al., Nature 320:275-277 (1986)), there is the potential of initiating a chronic retroviral infection in the host animal. (Page 4, line 16, through page 5, line 4.)

The specification supports new claim 104 as shown by the following claim chart:

<u>Claim</u>	<u>Applicant's Disclosure</u>
104. A method of transferring a gene into a recipient subject, comprising:	<p>This invention relates to a technique for altering the level of gene expression which involves the introduction of a genetically engineered cell into a recipient individual. (Page 1, lines 3-6.)</p> <p>The introduction of a transfected cell into a recipient subject is herein referred to as "transkaryotic implantation." (Page 16 at lines 26-28.)</p> <p>Figure 1 shows a diagrammatic representation of one embodiment of transkaryotic implantation. Cultured cells are co-transfected with the gene of therapeutic interest and a gene encoding a selectable marker. * * *</p> <p>A clonal line possessing the desired expression properties is then introduced into one of a variety of anatomical locations in the host animal, which is itself characterized with respect to expression of the gene of interest. (Page 12, line 22, through page 13, line 65).</p>
(a) providing somatic cells;	<p>Thus, transgenic therapy involves altering an animal's germ line in a manner which changes the genetic content of each of the animal's cells. In contrast, transkaryotic therapy involves somatic cells and does not alter the genetic content of the animal's cells. (Page 36 at lines 22-25.)</p>
(b) transfecting said somatic cells <i>in vitro</i> with a DNA sequence	<p>In a somatic cell gene delivery system, cells from the patient are removed,</p>

comprising said gene and a promoter capable of functioning in said somatic cells, wherein said gene encodes a gene product,

and wherein said somatic cells are stably transfected with said gene by integration of the gene into the chromosomes of the somatic cells or in replication competent extrachromosomal plasmids to impart to said somatic cells the permanent capacity to direct expression of said gene upon induction of said promoter;

cultured in vitro, transfected, and reimplanted. (Page 3, lines 13-16.)

In order to accomplish gene expression, it is necessary that the structural sequences of the desired of [sic, or] effector gene be operably linked to a promoter region. (Page 18, lines 28-31.)

Thus, any promoter capable of functioning in the transfected cell can be operably linked to the desired or effector gene sequence and used to express the gene in the transkaryotic cell. (Page 19, lines 13-16.)

[Original claim] 3. The method of any one of claims 1-2 wherein said desired or effector gene sequence is operably linked to a constitutive promoter region. (Page 62, lines 20-22.)

[Original claim] 4. The method of any one of claims 1-2 wherein said desired or effector gene sequence is operably linked to a regulatable promoter region. (*Id.* at lines 23-25.)

If such sequences integrate into the chromosome of the transfected cell or are able to replicate as extrachromosomal plasmids, then the cell may acquire the permanent capacity to direct the expression of the introduced, genetic sequence. Such a cell is said to be "stably transfected." (Page 33, lines 13-18.)

Since such cells acquire the permanent capacity to express the introduced genetic sequence, it would be preferable to employ stably transfected cells in situations in which one desired to provide the recipient subject with a

(c) screening the resulting transfected somatic cells *in vitro* to select a transfected somatic cell, wherein said screening comprises characterizing said transfected somatic cell with respect to expression and regulation of the gene by assaying for translation of the mRNA into the gene product;

(d) cloning and expanding, *in vitro*, the transfected somatic cell selected in step (c) to form 10^5 - 10^{10} transfected somatic cells;

prolonged capacity to produce the desired or effector gene product. (*Id.* at lines 18-24.)

Individuals [sic, Individual] colonies of stably transfected cells are then multiplied and characterized with respect to the expression and regulation of the gene of therapeutic interest. (Page 12, line 30, through page 13, line 2.)

The transfected cells should be fully characterized before implantation into the patient (Page 20, lines 26-28.)

The term "expression" as used herein refers to the ability of a cell to direct the transcription of a genetic sequence into mRNA, the translation of the mRNA into protein and the secretion of the protein out of the cell. Secretion of gene products may occur naturally or may be obtained by operably linking the desired or effector gene to a secretory signal sequence. Expression is said to be "normal" if it occurs at a level within accepted norms for that particular gene product in a particular species, or if the level of expression is essentially equivalent to that observed in untreated subjects of the same species as the recipient subject. (Page 18, lines 3-15.)

Individuals [sic, Individual] colonies of stably transfected cells are then multiplied and characterized with respect to the expression and regulation of the gene of therapeutic interest. A clonal line possessing the desired expression properties (Page 12, line 30 - page 13, line 6).

(e) combining the 10^5 - 10^{10} transfected somatic cells with a physiologically acceptable buffer or carrier; and

(f) injecting the resulting transfected cell preparation into the recipient subject,

wherein, following injection into the recipient subject, the clonal cells are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject.

After transfection, it is preferable to allow the transfected cells to proliferate and to then provide between 10^5 - 10^{10} cells to each recipient subject. (Page 36, lines 26-29.)

A "transfected cell preparation" is a suspension of cells, which contains at least one transfected cell, either (1) in a physiologically acceptable buffer or carrier or (2) within a physiologically acceptable container. (Page 16, lines 29-33.)

Figure 2 shows the amount of human growth hormone detected in the bloodstream of mice which had received intraperitoneal injections of either transiently transfected (dashed lines) or stably transfected (solid lines) cells. (Page 13, lines 7-11.)

Introduce Cells Into Desired Anatomical Location. (Fig. 1.)

In the past few years, it has become apparent that the implementation of retroviral based gene delivery systems in humans will face major obstacles, primarily related to properties of retroviruses themselves (Robertson, M., Nature 320:213-214 (1986), Marx, J.L., Science 232:824-825 (1986)).

* * *

Third, as recombination between the replication-deficient retroviruses utilized for the infection and the endogenous retroviruses present in mammalian genomes is known to occur (Hock, R.A. et al., Nature 320:275-277 (1986)), there is the potential of initiating a chronic retroviral infection in the host animal. (Page 4, line 16, through page 5, line 4.)

The use of viral vectors suffers from their potential for rearrangement of endogenous genes (Page 6, lines 27-31.)

Additional passages from the specification also support amended claim 72 and new claim 104, but Applicant does not cite them here for sake of brevity.

Interview Summary

Applicant thanks the Examiner for the telephone interview of August 19, 1999, with the undersigned. During that interview, the new Examiner and the undersigned agreed that, rather than have an actual interview at the present time, Applicant would submit the present Amendment, and the Examiner would grant an interview before issuing a subsequent Office Action. The new Examiner and the undersigned also agreed that the Examiner would give Applicant an opportunity to submit a Supplemental Response, if desired, in response to the interview before the Examiner issued a subsequent Office Action.

The claimed invention

Before addressing Paper No. 20, Applicant first summarizes the claimed invention to expedite allowance of the pending claims. Applicant's claims are directed to a method of transferring a gene into a recipient subject, and they now recite (or depend from claims that recite) that "following injection into said recipient subject, said clonal cells are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject." Applicant has added this clause to the claims and removed the clause

"wherein the DNA sequence comprises no DNA of retroviral origin, wherein the DNA sequence comprises the gene and a promoter operably linked to the gene." Applicant has also removed the phrases "without using a viral vector" (see previous claim 72), "without using a retroviral vector" (see previous claim 87), "without using viral infection" (see previous claim 102), and "without using retroviral infection" (see previous claim 103). Applicant has deleted these phrases and clauses. Nevertheless, Applicant believes that the new claim language encompasses these phrases and clauses.

Amended claim 72 also recites "chemical or physical techniques." Since, as the specification discusses, "rearrangement of endogenous genes and initiating chronic viral infection in said recipient subject" are inherent problems with viral techniques, using chemical or physical techniques necessarily results in cells that are incapable of these functions. (See page 4, line 16, through page 5, line 7; page 6, lines 27-31.)

Applicant's method uses nonviral techniques, resulting in cells that are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject. Such a method can be used to prepare cells for nonviral *ex vivo* gene therapy.

**New matter objection to claims 72-80, 82-85,
and 97-103 and written description rejection
of claims 72-80, 82-85, and 97-103 under
35 U.S.C. § 112, first paragraph**

The Examiner objected to the Amendment of December 8, 1998, as allegedly introducing new matter into the disclosure in the form of amended claims 72 and 87 and new claims 102 and 103 (Paper No. 20 at 2) and rejected claims 72-80, 82-85, and 97-

103 as allegedly not being supported by an adequate written description. (Paper No. 20 at 5.) Specifically, the Examiner contends that the recitations "without using a viral vector," "without using a retroviral vector," and "no DNA of retroviral origin" are not supported by an adequate written description and constitute new matter.

Applicant respectfully traverses the objection and rejection. Applicant maintains that the Examiner has not thoroughly analyzed and discussed the Goodman Declaration, see M.P.E.P. § 2163.04, has generally applied an impermissible literal support standard, see M.P.E.P. § 2063.03, and has erroneously asserted that negative limitations require literal support. Solely to expedite allowance of the pending claims, however, Applicant has deleted the objected to phrases from the claims and substituted therefor "following injection into said recipient subject, said clonal cells are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in said recipient subject." The above claim charts show that the specification uses this very terminology and, thus, supports it.

The Goodman Declaration also shows how the specification would have reasonably conveyed to one skilled in that art that Applicant invented a method of using clonal cells that "are incapable of causing rearrangement of endogenous genes and initiating chronic viral infection in said recipient subject."

As Applicant has previously discussed, the written description requirement is directed to a "person skilled in the art." 35 U.S.C. § 112, first paragraph. Accordingly, the disclosure as filed must only reasonably convey to one skilled in the art that Applicant invented the claimed subject matter. *Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

As Dr. Goodman stated, as of Applicant's filing date, those skilled in the art believed that viral techniques, especially retroviral techniques, were the most promising techniques for *ex vivo* gene therapy. (Goodman Dec. at ¶ 8-9.) Groups studying retroviral techniques in particular were dominating (and continue to dominate) the field. (*Id.*) Against this focus on viral techniques, the specification discusses problems with viral and retroviral techniques at length, calling them "major obstacles." (*Id.* at ¶ 9.) These "major obstacles" concern the possibility that transfected clonal cells could cause recombination of an introduced DNA sequence with endogenous retroviral sequences and initiate chronic viral infection in the recipient subject. (*Id.* at ¶¶ 10, 17-19.)

Dr. Goodman stated that, in light of the belief of those skilled in the art that these obstacles could be easily overcome, the specification's lengthy discussion of these obstacles and its characterization of them as "major" would have indicated to one skilled in the art that, unlike others, Applicant contemplated using a different method so that Applicant could avoid these obstacles—obstacles that Applicant (and few, if any, others) believed were major. (*Id.* at ¶¶ 20, 23, 25.)

In other words, the specification would have reasonably conveyed to one skilled in the art that Applicant invented the claimed subject matter by discussing these "major obstacles" with viral techniques and then discussing and successfully using a transfected cell preparation that is not subject to these obstacles. The specification reasonably conveyed to one skilled in the art that Applicant invented the claimed subject matter.

The Examiner also relied upon Applicant's use of plasmid pXGH5, which allegedly contains viral DNA, to support the objection and rejection. (Paper No. 20 at 4.) Applicant respectfully submits that this is no longer an issue in light of the claim amendments.¹ The objection and rejection, therefore, should be withdrawn.

Enablement rejection

The Examiner rejected claims 72-80, 82-85, and 97-103, under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification.² Specifically, the Examiner asserts that the specification does not enable the claimed invention because it does not discuss a "vector that contains no viral and/or no retroviral genetic material." (Paper No. 20 at 5-6.)

Applicant respectfully traverses this rejection. As with the written description rejection, Applicant respectfully submits that the claim amendments render this rejection moot.

¹ Moreover, Applicant showed at pages 8-10 of the Amendment of December 8, 1998, that neither plasmid pXGH5 nor pHINT5, which Applicant used in the Examples, were a viral vector or a retroviral vector, and that neither contained any DNA of retroviral origin. The Examiner did not address this argument in Paper No. 20, merely stating, erroneously, that plasmid pXGH5 contains viral DNA.

² The Examiner also states in this "Enablement" section of the Office Action that claims 72-80, 82-85, and 97-103 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being supported by an adequate written description. (Paper No. 20 at 5, lines 17-20.) Since Applicant already addressed this rejection above, he will not repeat those arguments here.

The remainder of the Enablement Section of the Office Action (page 7, line 7, through page 11, line 22) appears to be a copy of pages 5-8 of the Office Action of June 8, 1998 (Paper No. 16), and, thus, does not even mention, much less address, Applicant's intervening responses of June 25, 1998, and December 8, 1998. Nor does it address the basis for the present enablement rejection—the Examiner's erroneous assertion that the specification only uses a vector containing viral DNA. Accordingly, Applicant respectfully submits that the remainder of the Enablement Section is irrelevant to the present enablement rejection. If the new Examiner disagrees, Applicant respectfully requests that the Examiner so inform the undersigned at the Interview so that issuance of a Supplemental Office Action addressing the enablement arguments in the responses of June 25, 1998, and December 8, 1998, can be discussed.

For the above reasons, Applicant respectfully requests that the enablement rejection be withdrawn.

Obviousness type provisional double patenting rejections

The Examiner provisionally rejected claims 72-80, 82-85, and 97-103 under the judicially created doctrine of obviousness type double patenting over: (1) claims 91-126 of copending Application Serial No. 08/461,292; (2) claim 44 of copending Application Serial No. 08/460,902; (3) the pending claims of copending Application Serial No. 08/465,582; (4) the allowed claims of copending Application Serial No. 08/451,894; (5) claims 68-77 and 105-107 of copending Application Serial No. 08/446,909; (6)

claims 96-104 of copending Application Serial No. 08/446,912; and (7) claims 125-134 of copending Application Serial No. 08/443,936. (Paper No. 20 at 11-14.)

Applicant respectfully traverses these provisional rejections. Although these rejections are provisional, Applicant includes the following remarks regarding the provisional rejections over Application Serial No. 08/465,582 ("the '582 application") and Application Serial No. 08/460,902 ("the '902 application") in this Amendment, which begins Applicant's last available round of prosecution under 37 C.F.R. § 1.129(a), because the claimed invention clearly constitutes a separately patentable invention from that claimed in the '582 application, which is the application in the interference, and the '902 application, whose only pending claim is identical to the only claim in the '582 application.

The pending claims in the present application concern a species of the generic concept of *ex vivo* gene therapy claimed in the '582 and '902 applications, namely, *ex vivo* gene therapy using nonviral techniques.³ As Applicant showed above, the pending claims define this species by reciting that the clonal cells "are incapable of causing rearrangement of endogenous genes and initiating chronic viral infection in said recipient subject." Since these functions are the major obstacles with viral techniques and are not problems with chemical or physical techniques, using chemical or physical

³ Applicant's claims are directed to a method of transferring a gene into a recipient subject, which method is a nonviral technique. This method can be used to prepare cells for nonviral *ex vivo* gene therapy.

techniques necessarily results in cells that are incapable of these functions. (See Specification at page 4, line 16, through page 5, line 7; page 6, lines 27-31.)

A generic disclosure does not necessarily render a species within that genus obvious. *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). This is especially true when prior art teaches away from the claimed species. *Id.* Applicant has submitted numerous references showing that those of ordinary skill in the art did not have a reasonable expectation of success using nonviral techniques, as evidenced by their having considered and then dismissed such techniques in favor of viral techniques. Since the prior art's teaching that Applicant should not do what Applicant did is "a fact strongly probative of nonobviousness," *Kloster Speedsteel AB v. Crucible, Inc.*, 230 U.S.P.Q. 81, 86 (Fed. Cir. 1986), the generic claims of the '582 and '461 applications do not render the claimed specific invention obvious.

Gene transfer, the first step of *ex vivo* gene therapy, can be carried out in two different ways: (1) viral techniques or (2) nonviral techniques. Viral techniques involve genetically engineering a viral vector to contain the foreign gene and then exposing cells to the viral vector. Nonviral techniques include chemical techniques, such as calcium phosphate transfection, and physical techniques, such as microinjection, electroporation, and fusion.

The pending claims recite a method of transferring a gene into a recipient subject using clonal cells that are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject. Such cells necessarily are not obtained by viral techniques. The

generic claims of the '582 and '902 applications do not suggest such a specific method because the prior art taught away from this species.

Prior to Applicant's invention, nonviral techniques had not been used successfully, and those of ordinary skill in the art did not consider them to be suitable for *ex vivo* gene therapy. Those of ordinary skill in the art thought that *ex vivo* gene therapy required a highly efficient method of introducing a gene into a cell and that such high efficiencies could only be obtained with viral techniques, especially retroviral techniques.

A gene therapist summarized the belief those of ordinary skill in the art held in the early and mid-1980s, prior to Applicant's invention. (*Transcript of the FDA Biological Response Modifiers Advisory Committee Meeting of December 13, 1990*, 51-57.)⁴ He discussed the inefficiencies of nonviral techniques as a gene transfer method and stated that these inefficiencies had led those of ordinary skill in the art to use retroviral techniques:

So a variety of other techniques have been studied, all of them suffering from this relatively low level of efficiency. So about a dozen, 8 or 10 years ago [about 1978, 1982, or 1980] the field evolved into studying the possibility of using recombinant retroviruses and vectors for transferring genes.

(*Id.* at 57.)

⁴ Applicant has previously submitted all references he cites in this Amendment. If the new Examiner has any difficulty finding these references in the file, Applicant invites her to contact the undersigned.

At the first gene therapy conference in 1983, one of the participants discussed chemical and physical techniques of gene transfer and promptly dismissed them all as being inadequate for *ex vivo* gene therapy. (Friedmann, T., *Gene Therapy: Fact and Fiction in Biology's New Approaches to Disease* 39 (1994).) He then went on to discuss the merits of viral techniques for gene insertion. According to him, viral transduction "is, I think, the way to go." (*Id.* at 40.)

In a seminal gene therapy article in 1984, W. French Anderson discussed various gene transfer techniques. (Anderson, at 402, col. 2.) Anderson concluded that retroviral techniques were the most promising gene transfer technique:

As noted, retroviral-based vectors appear to be the most promising approach at present for use in humans.

(*Id.* at 504.)

In a review article in 1986, Gilboa et al. discussed nonviral transfection as a gene transfer technique and concluded that retroviral techniques were the best gene transfer method for *ex vivo* gene therapy. (Gilboa et al., *Transfer and Expression of Cloned Genes Using Retroviral Vectors*, 4 *BioTechniques* 504 (1986).) Gilboa et al. first dismissed nonviral transfection as a gene transfer method:

Unfortunately, DNA transfection has its limitations. Most significantly, it is a very inefficient means of transferring genes into mammalian cells A second important issue is one of expression--once delivered, how to ensure the proper expression of the gene in the recipient cell.

(*Id.*) They then discussed the superiority of retroviral techniques as *ex vivo* gene transfer methods:

In the past several years, a new gene transfer technology has emerged which appears to be superior to DNA transfection and other previous techniques and which may offer a new approach to the therapy of human genetic diseases. This new technology is known as retroviral-mediated gene transfer, i.e., the use of retroviruses to deliver genes into cells.

(*Id.*; internal footnote omitted.)

In a 1987 review article, Caskey discussed the inefficiencies of nonviral techniques as a gene transfer methods. (C. Thomas Caskey, *Genetic Therapy: Somatic Gene Transplants*, 22 Hospital Practice 181, 184-85 (1987).) According to Caskey, results with non-retroviral techniques showed that "effective gene therapy will require far more efficient techniques of gene transplantation An obvious alternative is to use viruses as vectors, as we use bacteriophage vectors to insert genes into bacteria for cloning." (*Id.* at 185, col. 1.)

Even after Applicant's U.S. filing date, those skilled in the art who were not aware of Applicant's invention continued to believe that viral techniques were necessary for *ex vivo* gene therapy. This is in contrast to the numerous references Applicant discussed in the Amendment of May 26, 1998, that considered Applicant's work and recognized it as novel and pioneering.

For example, in a 1988 review article, Eglitis et al. discussed various techniques other than viral techniques. (Eglitis et al., *Retroviral Vectors for Introduction of Genes into Mammalian Cells*, 6 BioTechniques 608 (1988).) Eglitis et al. dismissed each of these techniques because "they each suffer from limitations affecting their general applicability." (*Id.*) Eglitis et al. then discussed the improved efficiency of retroviral

techniques, and they concluded that retroviral techniques were the best gene transfer method for *ex vivo* gene therapy:

Nonetheless, retroviruses still appear to be the best technology so far available for the transfer of clinically relevant genes

(*Id.* at 613, col. 1.)

In a 1989 review article, Kohn et al. also discussed various physical and chemical techniques. (Kohn et al., *Gene Therapy for Genetic Diseases*, 7 *Cancer Investigation* 179, 183 (1989).) Kohn et al. dismissed each of these techniques because each "has limitations that make them unsuitable for human gene therapy at present." (*Id.*) Kohn et al. then devoted the remaining eight pages of the article, including a section devoted to "future prospects," to retroviral vectors. (*Id.* at 184-91.)

In a 1990 review article, Verma also discussed chemical and physical techniques and dismissed each of these methods as being inefficient. (Verma, I. M., *Gene Therapy*, *Scientific American* 68, 69-70 (November 1990).) Verma then devoted the remaining six pages of the article to retroviral techniques because "retroviruses are the most promising gene-delivery system supplied thus far" (*Id.* at 70, col. 1.)

In a 1992 article, Rosenberg discussed various chemical and physical techniques and noted the low efficiencies of these techniques. (Rosenberg, S., *Gene Therapy for Cancer*, 268 *JAMA* 2416, col. 3 (1992).) According to Rosenberg, these low efficiencies had caused those of ordinary skill in the art to turn to viral techniques for gene transfer:

Because of the need for high-efficiency transfer of DNA into cells for clinical applications, attention has increasingly turned to the use of viruses, especially transforming DNA viruses such as papoviruses, adenoviruses, or more recently murine and avian retroviruses as delivery systems.

(*Id.*) Rosenberg concluded that "retroviruses, especially those based on the Moloney murine leukemia virus, are now being used in clinical applications." (*Id.* at 2417, col. 1.)

In a 1993 article, Rosenberg et al. stated that, despite the existence of many techniques, only retroviral techniques were practical:

Although many methods exist for introducing foreign genes into cells, the only method with sufficient efficiency for practical use in human trials involves the use of genetically engineered retroviruses.

(Rosenberg, S.A., et al., *The Development of Gene Therapy for the Treatment of Cancer*, 218 Ann. Surg. 455 (1993).) Indeed, Rosenberg et al. asserted that *ex vivo* gene therapy was impossible until retroviral vectors had been improved enough to transduce cells at a high efficiency:

The recent development of high-efficiency techniques for gene transduction using retroviruses has made the treatment of human diseases by gene transfer techniques a realistic possibility.

(*Id.* at 455, col. 1.)

Not one of these references after Applicant's filing date considered Applicant's work. Thus, those of ordinary skill in the art did not expect that nonviral techniques would work. Moreover, unlike those who have considered Applicant's work and recognized it as pioneering, those who have not considered Applicant's work continue

to expect that nonviral techniques will not work and that viral techniques are necessary for *ex vivo* gene therapy. As Dr. Goodman discussed:

8. Prior to 1987, nonviral gene transfer methods had not been used successfully for gene therapy, and those skilled in the art came to the conclusion that such methods were unsuitable for *ex vivo* gene therapy. Those skilled in art thought that *ex vivo* gene transfer for gene therapy required a highly efficient method of introducing a gene into a cell. They believed that the inherent inefficiency of nonviral gene transfer methods presented an obstacle that made their successful use in *ex vivo* gene therapy unlikely. (Ex. 2 at 405, cols. 1 and 3, 406, col. 1; Ex. 3 at 213, col. 2).

9. Rather than nonviral methods, those skilled in the art, at the time of the filing of the Selden application, believed that viral transduction, especially retroviral transduction, was the best method for *ex vivo* gene therapy. (Ex. 2 at 408, col. 1). More efficient retroviral vectors were being developed, and the groups developing these vectors and studying retroviral transduction were dominating (and, indeed still dominate) the field of *ex vivo* gene therapy. This belief was so dominant that almost the entire field focused on retroviral transduction to the exclusion of less efficient nonviral methods.

(Goodman Dec. at ¶¶ 8-9.)

Notwithstanding the technical obstacles to nonviral techniques and the belief of those skilled in the art that these obstacles required the use of viral techniques, Applicant surprisingly discovered a method for *ex vivo* gene transfer that does not use viral techniques, resulting in clonal cells that are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject. Since those of ordinary skill in the art expected that such a techniques would fail, the generic claims of the '582 and '902 applications cannot render the claimed invention obvious.

**Indefiniteness rejection of claims 72-80, 82-85,
and 87-103 under 35 U.S.C. § 112, s cond paragraph**

The Examiner rejected claims 72-80, 82-85, and 87-103 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite on several grounds. (Paper No. 20 at pages 14-16.) Applicant respectfully traverses this rejection and submits that the amendments render this rejection moot.

**Provisional rejection of claims 72-80, 82-85,
and 87-103 under 35 U.S.C. §§ 102(f), (g), or 103**

The Examiner provisionally rejected claims 72-80, 82-85, and 97-103 under 35 U.S.C. §§ 102(f), (g), or 103 as allegedly being unpatentable over the count and disclosure of the winning party in the interference. (Paper No. 20 at 17.)

Applicant respectfully traverses this provisional rejection. The count in the interference is identical to the pending claims in the '582 and '902 applications. As Applicant discussed above regarding the provisional obviousness-type double patenting rejections, the generic claims of the '582 and '902 applications (and the count of the interference) cannot render the claimed invention obvious because the prior art taught away from this species of the claims by expressly dismissing it as a possibility.

Regarding the §§ 102(f) and 102(g) rejections, the Examiner has never asserted that the disclosures of the other parties in the interference teach or enable using nonviral *ex vivo* techniques. Since the Examiner has not asserted that the disclosures of the other parties in the interference teach or enable using nonviral *ex vivo* techniques, resulting in cells that are incapable of causing recombination of the DNA

sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject, Applicant respectfully requests withdrawal of these § 102 rejections as well.

**Rejections of claims 72-75, 78-80, 82-90, 93-95,
and 97-103 under 35 U.S.C. § 103(a)**

The Examiner rejected claims 72-75, 78-80, 82-90, 93-95, and 97-103 under 35 U.S.C. § 103(a) as allegedly being obvious over Salser et al. and Anderson (Paper No. 20 at 13), and the Examiner rejected claims 76-77 and 91-92 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the same references in view of Sugimoto. (Paper No. 20 at 19.) Applicant respectfully traverses these rejections and addresses them together because they fail for the same reasons.

Salser et al. does not teach or suggest "cloned and expanded somatic cells," despite the Examiner's assertion to the contrary. (Paper No. 20 at 18, lines 29-30.) The Salser et al. patent describes removing cells from an animal, transfecting them *in vitro* with a *dhfr* gene, the product of which confers methotrexate resistance, and then introducing the transfected cells into an animal. Methotrexate is then administered to the animal, and, according to the patent, it kills the competing, non-transfected cells, allowing the transfected cells to proliferate. The Salser et al. patent does not teach or suggest the selected and cloned cells of the claimed invention.

Even the Examiner does not assert that Salser et al. teaches or suggests "a cloned and selected cell" and cloning and expanding "the selected somatic cell," as the claims recite. Rather, the Examiner asserts that Salser et al. teaches "maintaining the

[transfected] **cells** *in vitro* (*i.e.*, cloning and expanding the **cells**) . . . to culture the **cells** *in vitro* and . . . selecting **cells**" (Paper No. 20 at 18-19; emphasis added.)

Moreover, to the extent Salser et al. teaches any selection, it occurs *in vivo*, not *in vitro* as the claims recite. Salser et al. transfected cells and introduced the transfected cells into an animal. Only then did Salser et al. attempt any selection by administering methotrexate to the animal.

Anderson also does not teach a transfected cell preparation comprising cloned and expanded cells, nor does Sugimoto et al., and the Examiner has not alleged otherwise.

Furthermore, as Applicant discussed above regarding the provisional obviousness type double patenting rejections, the pending claims concern a species of the generic concept of *ex vivo* gene therapy, namely nonviral *ex vivo* gene therapy. The claim of the '582 application is generically directed to *ex vivo* gene therapy, and the Examiner necessarily found that claim to be patentable over the prior art for it to be involved in an interference. See 37 C.F.R. § 1.603. Applicant fails to understand how the Examiner can reject the pending species claims over the prior art when the Examiner has already determined that the generic claim of the '582 application was patentable over the same prior art, especially when it is easier for prior art to render a genus unpatentable than for prior art to render a species unpatentable. *Compare*. M.P.E.P. § 2131.02 ("A species will anticipate a claim to a genus") with M.P.E.P. § 2144.08 ("The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.").

As Applicant also discussed above regarding the provisional obviousness type double patenting rejections, no references taught or suggested using nonviral techniques, resulting in cells that are incapable of causing recombination of the DNA sequence with endogenous retroviral sequences and initiating chronic viral infection in the recipient subject, as the claims recite. Indeed, numerous references taught away from the claimed invention. Applicant will not repeat those arguments here. However, especially important to these rejections is the teaching away of the Anderson reference.

References must be considered for all that they teach, including any teaching away from the claimed invention. M.P.E.P. § 2141.02. The Examiner relies on the Anderson reference, but the Anderson reference actually teaches away from the claimed invention by advocating viral techniques, especially retroviral techniques. For example, "Chemical Techniques" are discussed, but the results are said to "appear discouraging" (Anderson at 405, col. 1, first complete paragraph.) With respect to "Physical Techniques," electroporation is dismissed ("uncertain"), microinjection of stem cells is dismissed ("not feasible"), and microinjection of fertilized human eggs is dismissed ("Consequently there would be little use of the procedure even if it were available. A different approach for human gene therapy is required"). (Anderson at 405.) "Viral Techniques," however, especially retroviral techniques, are not dismissed and are considered the most promising techniques. (Anderson at 402-404; 408, col. 1.) Thus, Applicant respectfully submits that the cited Anderson reference actually evidences the nonobviousness, not the alleged obviousness, of the claimed invention.

None of the cited references, alone or in combination, teaches the claimed invention; none of the cited references, alone or in combination, provides any motivation to combine them; and none of the cited references, alone or in combination, provides any expectation of success. Accordingly, Applicant requests withdrawal of the obviousness rejections.

Conclusion

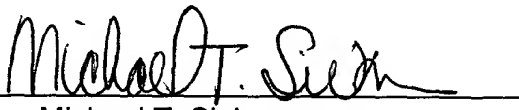
In view of the extensive evidence of the nonobviousness, description, and enablement of the claimed invention, Applicant respectfully submits that the claims are in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Date: October 5, 1999

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